Has Progress Been Made in Progressive Myoclonic Epilepsy (EPM1)?

Refining the Phenotype of Unverricht-Lundborg Disease (EPM1): A Population-Wide Finnish Study.

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OBJECTIVE: This Finnish nationwide study aimed to refine the clinical phenotype variability and to identify factors that could explain the extensive variability in the clinical severity of the symptoms observed among patients with Unverricht-Lundborg disease (progressive myoclonus epilepsy type 1 [EPM1]) homozygous for the dodecamer expansion mutation in the cystatin B (*CSTB*) gene. METHODS: The study population consisted of 66 (33 men and 33 women) patients with genetically confirmed EPM1 homozygous for the *CSTB* expansion mutation for whom the sizes of the expanded alleles were determined. The clinical evaluation included video recorded Unified Myoclonus Rating Scale and retrospectively collected medical history. The navigated transcranial magnetic stimulation test was used to determine motor threshold (MT) and silent period (SP) of the motor cortex. RESULTS: An earlier age at onset for EPM1 and longer disease duration were associated with more severe action myoclonus, lower performance IQ, increased MT, and prolonged SP. The number of dodecamer repeats in *CSTB* alleles varied between 38 and 77. On average, the size of the longer expanded alleles of patients was independently associated with MT, but exerted only a modulating effect on age at onset, myoclonus severity, and SP. CONCLUSIONS: As a group, earlier disease onset and longer duration are associated with more severe phenotype. Even though the vast majority of patients with EPM1 have a uniform genetic mutation, the actual size of the longer *CSTB* expansion mutation allele is likely to have a modulating effect on the age at disease onset, myoclonus severity, and cortical neurophysiology.

Commentary

Unverricht-Lundborg disease (progressive myoclonic epilepsy type 1 [EPM1]) is a rare autosomal recessive neurodegenerative disorder caused by unstable dodecamer repeats of the cystatin B gene (*CSTB*). Presenting in early childhood (6–15 years) with stimulus-induced myoclonus and tonic-clonic seizures, the neurologic exam may be normal at onset, though the disease inevitably progresses to include ataxia, dysarthria, intention tremor, and incoordination, along with psychologic manifestations of depression, emotional lability, and decline in intellectual function over subsequent years (1). While rare, EPM1 is the most common of the progressive myoclonic epilepsies, with the highest incidence (1/20,000) in the Finnish population, making this cohort prime for investigating the disease (2, 3). The phenotype of EPM1 can vary with regard to age of onset, severity of seizures and myoclonus, and rate of deterioration, even within the same family or among individuals with similar size repeat expansions of *CSTB* (1, 4). Hyppönen and colleagues refine the characteristics of EPM1 and further identify factors responsible for this phenotypic variability through investigation of the largest reported genetically confirmed cohort of EPM1.

The authors collected basic disease demographics in addition to *CSTB* expansion size, measurements of cortical excitability using motor threshold (MT), a measurement of cortical hyperexcitability, and silent period, a measure of cortical inhibition ,via transcranial magnetic stimulation, and severity of myoclonus using a standardized unified myoclonus rating scale. They demonstrate that earlier age of onset and longer duration of disease most significantly account for variable severity of myoclonus across patients. As the study was a cross-sectional design with group analysis, they are cautious to extrapolate data to a single patient, as even patients with identical age of onset had varied symptoms. Whether this reflects an inherent difference in disease severity or simply collection of data at a different point in disease progression is not clear. EPM1 symptoms progress over the first 5 to 10 years before plateauing, therefore collection of data at a single point in time among patients with different durations of disease did not allow delineation of which characteristic is most predictive of symptom severity. Thus, while this study may not help predict speed of symptom progression, we do gain insight into negative predictive characteristics. The linear correlation between disease duration and severity of myoclonus suggests earlier onset will likely result in attainment of disabling

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symptoms at a younger age, which may explain the additional adverse effect on performance IQ seen in those with more severe myoclonus. While these patient characteristics predict poor outcome, they cannot fully explain the clinical variability seen in less affected patients with similar age of onset and duration of disease.

As *CSTB* expansion is the primary cause of EPM1 worldwide, the authors sought to investigate a connection between *CSTB* expansion size and symptom severity, a correlation refuted by prior smaller studies of EPM1 (4, 5). Many are familiar with triplet repeat diseases such as Huntington chorea or myotonic dystrophy in which symptom severity increases with each generation (anticipation) as the size of the repeat expands. Anticipation is generally not seen in autosomal recessive disease, as all affected individuals are offspring of clinically unaffected carrier parents (4). However, repeat size may still influence symptom severity, as occurs in Freidreich ataxia, another recessive repeat disease (6, 7). In the present study, longer *CSTB* repeat size corresponds with an earlier onset of disease, but only when a single patient with late onset of symptoms and small repeat size are included in the analysis. It is possible that as the EPM1 cohort grows, delineation of a connection between *CSTB* repeat size and clinical severity will arise, but for now it does not appear to have a direct correlation.

While there was no independent effect of genetic variation on clinical phenotype, the *CSTB* expansion size may still have a modulating effect on symptoms. The authors found a correlation between longer *CSTB* expansions and higher MTs, prolonged silent period, and severity of myoclonus. MT is expected to be lower in untreated patients with EPM1, indicating cortical hyperexcitability leading to myoclonus. The authors demonstrated higher MTs associated with longer *CSTB* expansions, a finding possibly attributed to the increased number of antiepileptic drugs (AEDs) used in more severe cases. Despite exposure to several AEDs, patients continued to have myoclonus, a finding cited in a previous study, which included many patients from this cohort and concluded that elevated MT could not be interpreted to indicate reduced cortical excitability (8). Theoretically, it would appear that the prolonged MT is not an etiology of more severe myoclonus, but instead a manifestation of more severe phenotype. Longer silent period durations represent increased inhibitory action. While a prolonged silent period was a strong indicator of myoclonic severity, this too appears less likely to be a neurophysiologic cause and instead a reaction to severe myoclonus. Thus, these findings suggest that longer *CSTB* repeats are related to altered neurophysiologic networks but are more likely to exert a modulating effect instead of being an independent cause of phenotype severity.

The disconnection between allele size and EPM1 symptoms remains unclear. It is possible that allele size reaches a critical threshold after which time *CSTB* expression is reduced, resulting in symptoms (5). Compared with the expansion found in Freidreich ataxia, which decreases frataxin proportional to repeat length and thus increases severity, the dodecamer repeat of EPM1 may reside between promotor regions, which simply become inactive once a critical distance is surpassed (9, 10). Once *CSTB* is reduced, other as yet unknown genetic factors may be influenced to varying degrees and result in phenotypic variability.

In the end, we are left without a direct correlation between *CSTB* expansion size and disease severity, a finding which would prove immensely useful in providing prognosis and guiding treatment in patients with EPM1. In a rare disease with phenotypic variability, it is difficult to characterize subtypes of the disease with such small numbers of affected individuals. This cohort utilizes an increasing patient population to delineate several characteristics that correlate to more severe outcome and provides evidence that other modifying factors remain at play in this disorder. While progress has certainly been made in EPM1, only with time and more patients will our understanding improve.

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References

1. Lehesjoki A-E, Kälviäinen R. Unverricht-Lundborg Disease. In: *GeneReviews (Internet)*. (Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird, TD, Fong C-T, Smith RJH, Stephens K, eds.) Seattle: University of Washington; 1993–2015. http://www.ncbi.nlm.nih.gov/books/NBK1142. Accessed May 27, 2015.
2. Berkovic SF, Andermann F, Carpenter S, Wolfe LS. Progressive myoclonic epilepsies: Specific causes and diagnosis. *N Engl J Med* 1986;315:296–305.
3. Norio R, Koskiniami M. Progressive myoclonic epilepsy: Genetic and nosological aspects with special reference to 107 Finnish patients. *Clin Genet* 1979;15:382–398.
4. Mazarib A, Xiong L, Neufeld MY, Birnbaum M, Korczyn AD, Pandolfo M, Berkovic SF. Unverricht-Lundborg disease in a five-generation Arab family. *Neurology* 2001;57:1050–1054.
5. Lalioti MD, Scott HS, Genton P, Grid D, Ouazzani R, M'Rabet A, Ibrahim S, Gouider R, Dravet C, Chkili T, Bottani A, Buresi C, Malafosse A, Antonarakis SE. A PCR amplification method reveals instability of the dodecamer repeat in progressive myoclonus epilepsy (EPM1) and no correlation between the size of the repeat and age at onset. *Am J Hum Genet* 1998;62:842–847.
6. Durr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, Mandel JL, Brice A, Koenig M. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996;335:1169–1175.
7. Montermini L, Richter A, Morgan K, Justice CM, Julien D, Castellotti B, Mercier J, Poirier J, Capozzoli F, Bouchard JP, Lemieux B, Mathieu J, Vanasse M, Seni MH, Graham G, Andermann F, Andermann E, Melançon SB, Keats BJ, Di Donato S, Pandolfo M. Phenotypic variability in Friedreich ataxia: Role of the associated GAA triplet repeat expansion. *Ann Neurol* 1997;41:675–682.
8. Danner N, Julkunen P, Khyuppenen J, Hukkanen T, Könönen M, Säisänen L, Koskenkorva P, Vanninen R, Lehesjoki AE, Kälviäinen R, Mervaala E. Altered cortical inhibition in Unverricht-Lundborg type progressive myoclonic epilepsy (EPM1). *Epilepsy Res* 2009;85:81–88.
9. Campuzano V, Montermini L, Lutz Y, Cova L, Hindelang C, Jiralerspong S, Trottier Y, Kish SJ, Faucheux B, Trouillas P, Authier FJ, Dürr A, Mandel JL, Vescovi A, Pandolfo M, Koenig M. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum Mol Genet* 1997;6:1771–1780.
10. Lalioti MD, Scott HS, Antonarakis SE. Altered spacing of promotor elements due to the dodecamer repeat expansion contributes to reduced expression of the cystatin B gene in EPM1. *Hum Mol Genet* 1999;8:1791–1798.